REMARKS

This response is submitted in reply to the Office Action mailed March 27, 2007 (" the Action"). Claims 1-88, 105 and 106 are pending in the application. New Claims 107-123 have been added. Of the pending claims, Claims 1-42 were withdrawn from consideration by the Examiner. Applicant has canceled Claims 1-42 without prejudice thereto subject to pursuit in a divisional application. Claims 43-88, 105 and 106 have been examined as being readable on the elected invention but stand rejected.

I. The §112, Second Paragraph, Rejections

The Action rejects Claims 70-76, 78-88 and 106 under 35 USC §112, second paragraph, as being indefinite because the "monitoring period of interest" during which the sampling is to occur is unspecified thus making it unclear what are the metes and bounds of the claims. Applicant respectfully disagrees.

Although Applicant believes that the claims are sufficiently clear as originally presented, Claims 70 and 106 have been amended to remove the objected to phrase to advance prosecution.

While not wishing to be bound to any particular mode of operation, in some embodiments, the period of interest can correspond to how long a therapeutic agent remains in the body after administration, such as, for example, 2-4 days for some chemotherapeutic agents (*see, e.g.*, p. 21, 27). The sampling period of interest can be standardized across patients or customized for each patient or combinations of these modes (*see*, p. 27). That is, a set period can be established or predefined as the monitoring or sampling period or the monitoring/sampling period can continue based on how long a detected *in situ* count is above a defined threshold.

In view of the foregoing, Applicant respectfully requests that the 35 USC §112, second paragraph rejections be withdrawn.

II. U.S. Patent Application Publication 2004/0011671 to Shults et al ("Shults")

Claims 43, 44, 46, 47, 54 and 105 stand rejected as being anticipated by Shults. Shults is directed to an implantable glucose sensor. As noted by the Examiner, Shults proposes that the sensor device can include a fluorescence sensor, such as that proposed by U.S. Patent No. 5,341,805 to Stavridi et al. ("Stavridi"). Note that Shults appears to mistakenly refer to the Stavridi patent document as "Colvin" although the last line of the section quoted below appears to reference the matrix with the fluorescent indicator molecules of Colvin. Regarding the fluorescence sensor, Shults states that:

> The invention of Colvin [Stavridi?] provides a method for incorporating an ultraviolet light source and fluorescent sensing molecules in an implantable device. However, Colvin [Stavridi?] does not describe how the sensor would survive harsh in vivo environmental conditions, how the device would be functionally integrated into body tissues or how a continuous supply of glucose would be maintained by the sensor. These problems may be solved by providing a low molecular weight filtrate of biological fluid in a controlled volume to the sensor.
>
> In this example, a continuous supply of biological glucose passes to the sensor through the angiogenic layer that prevents isolation of the sensor by the body tissue. The glucose is then filtered through the bioprotective membrane to produce a desirable filtrate having fewer interfering molecules and to protect the sensor from in vivo environmental conditions. Alternatively, a filtrate layer may be utilized having specific filtration properties to produce the desired filtrate. The three-dimensional structure of the bioprotective membrane and/or filtrate layer also provides stabilized sample volume for detection by the sensor.
>
> One skilled in the art would recognize that a fluorescence sensor requires a source of light. Consequently, the implantable device of the present invention would further comprise a source of radiation, as well as fluorescent sensing molecules to detect the presence of analyte.

Shults, (para. 56, 57, 58)(emphasis added).

Thus, Shults teaches that for an implantable fluorescence sensor to work in the body, the sensor must be configured to provide a controlled sample volume using a membrane and/or filtrate layer to provide a stabilized sample volume. Shults proposes

implanting the sensor in a location that allows the sensor interface to contact blood or interstitial fluid (para. 16) with the bioprotective membrane is permeable to oxygen and glucose (para. 22). Also, the last sentence quoted above, Shults appears to require fluorescent sensing molecules to detect the presence of analyte. While Applicant could not find further discussion of this feature in Shults, this appears to incorporate the fluorescent indicator molecules in the matrix or layer of Colvin, which is also very different from the instant invention as discussed below with respect to Colvin.

The stabilized sample volume configuration of Shults (with or without the indicator molecule layer of Colvin) is in contrast to the operation of the sensors of the instant invention, which, projects the light signal into tissue and detects the fluorescent response from the tissue, rather than in blood or plasma (*see, e.g.*, Figures 1A, 3, 9A, 9B, 10, etc... of the instant application). Clearly, in contrast to Shults, the implantable sensors of the instant invention do not require a stabilized sample volume and do not have a permeable membrane or filtrate layer to provide this feature as required by Shults. Out of completeness, Applicant notes that in some embodiments, the instant application does describe the use of light filters, but not sample filters.

Further, Applicant was unable to find any further discussion of fluorescent excitation or detection response wavelengths, LED operation, and the like, in Shults. Thus, Applicant submits that Shults, as modified by Stavridi, would have a fluorescence sensor that operates at the same LED glucose fluorescence excitation wavelengths as described by Stavridi.

Stavridi describes a glucose narrow band **fluorescence** excitation light at a wavelength between 250-350 nm, typically 308 nm (col. 1, lines 65-67) and the wavelength of the characteristic spectral peak of glucose fluorescence is between 335 to 355 nm (30-50 nm above the excitation light) (col. 2, lines 3-7). A second wavelength is used as a reference band and is between 380 nm to 420 nm (col. 2, lines 8-9) and reiterated at col. 5, lines 52-55. Applicant was unable to find where the second wavelength is a fluorescence excitation wavelength. Figures 2 and 3 of Stavridi are graphs of intensity of glucose (Figure 2) or plasma (Figure 3) versus wavelength when a

glucose sample is illuminated with a laser light at a wavelength of 308 nm. Again, Applicants believe that the second wavelength is not a fluorescence-excitation wavelength, but may invoke some type of light emission from the plasma or blood, potentially to standardize the intensity measurement for background signal. A ratio of intensity of the glucose and the reference intensity is used to determine glucose concentration (col. 5, lines 4-7).

In contrast, in certain embodiments of the instant invention, the detection systems and associated sensors can be configured to generate a fluorescent excitation light for fluorescent therapeutic analytes in tissue in the body and have a fluorescent excitation wavelength of at least about 400 nm, typically between about 400 nm to 900 nm as discussed at page 38 of the application (*see, e.g.*, Claims 106, 107).

Also, as recited in the pending claims, unlike Shults/Stavridi, an administered fluor-analyte in local tissue is used as to generate the fluorescence, it is not from a continuous supply of naturally occurring glucose in the body nor is the fluor-analyte in a filtrate or membrane on the sensor itself.

Applicant reiterates that while Stavridi does propose a light transmission at a wavelength in the range of 380-420 nm as a "reference" band, Applicant does not believe that this is a fluorescent excitation light nor that the reference light signal causes a fluorescence response, much less a fluorescent response of the glucose.

Applicant also submits that the system of Shults to be practicable, should take glucose measurements several times a day chronically (daily). In contrast, embodiments of the invention take measurements over a monitoring period of at least 24 hours to generate a time-response profile that is used to determine uptake and retention in local tissue. This information may be used to calculate a delivered dose or predict a receptiveness to therapy, etc. Unlike a continuous glucose supply whose concentration varies over time with the concentrations are typically determined several times a day, embodiments of the invention monitor fluorescence on a longer scale to determine when the local tissue no longer has the analyte, but with dormant periods as there is no "continuous" or ongoing supply of this fluor-analyte (see Fig 13E, Claims 46 and 117).

Claims 43 and 105 are restated below for ease of discussion.

43. A detection system for detecting fluorescence in a body of a subject associated with an administered fluorescent analyte, the fluorescent analyte including at least one of a fluor-labeled analyte, a naturally fluorescent analyte and an analyte that exhibits fluorescence when administered to the subject, the detection system comprising:

at least one fluorescence sensor configured for *in vivo* operation, the at least one sensor being configured to emit a fluorescent excitation light signal used to generate a fluorescent response of the fluorescent analyte in local tissue, with the fluorescent excitation light signal having a wavelength that is at least about 400 nm, and to detect fluorescence from the fluorescent analyte in the local tissue in the body in response to the emitted excitation light signal, at least intermittently, over a period of time extending for at least about 24 hours after administration of a fluorescent analyte to the subject, wherein the fluorescent analyte is administered from a source other than the at least one sensor; and

a processor operably associated with the at least one sensor configured to direct the output of the excitation signal and to receive fluorescence intensity signal data associated with the detected fluorescence of the administered analyte in response to the excitation light signal at the fluorescence excitation wavelength from the at least one sensor, wherein said processor is configured to monitor intensity over time associated with one or more of the uptake and retention of the fluorescent analyte in the local tissue at a plurality of points in time over at least one monitoring period.

105. A detection system for detecting fluorescence in a subject associated with an administered fluorescent analyte, the fluorescent analyte including at least one of a fluor-labeled analyte, a naturally fluorescent analyte and an analyte that exhibits fluorescence when internally administered to the subject, the detection system comprising:

at least one fluorescence sensor configured for *in vivo* operation, the at least one sensor being configured to emit an excitation light signal having a fluorescent excitation wavelength of at least 400 nm at a depth into local tissue at a tumor treatment site in the subject's body that is at least 2 mm and to detect fluorescence from a fluorescent analyte in the local tissue in response to the emitted excitation light signal, at least intermittently, over a period of time extending for at least about 24 hours after administration of a fluorescent analyte during each monitoring period, wherein the sensor is configured to detect fluorescence that is administered remote from the sensor itself or from a source that is independent of the sensor; and

> a processor operably associated with the at least one sensor configured to direct the output of the excitation signal and to receive fluorescence intensity signal data associated with the detected fluorescence in the local tissue from the at least one sensor, wherein said processor is configured to monitor intensity over time associated with one or more of the uptake and retention of the fluorescent analyte in the local tissue at a plurality of points in time over at least one monitoring period.

As Shults fails to teach or suggest at least the emphasized features in Claims 43 and 105, Applicant respectfully submits that for at least these features, Claims 43 and 105 are not anticipated by this reference and requests that these rejections be withdrawn.

III. U.S. Patent No. 6,330,464 to Colvin ("Colvin")

The Action rejects Claims 43-45, 54-56, 59-63, 65-69 and 105 as being anticipated by Colvin. The Action alleges that Colvin teaches the various features recited in the noted claims, *e.g.*, self-contained sensor, high pass filter, telemetric operation, subcutaneous size, LED sources and the like.

Colvin proposes a sensor with an integral matrix layer 14 coated over the exterior surface of the sensor body 12 (col. 2, lines 20-39). The matrix layer 14 has fluorescent indicator molecules 16 distributed through the layer. The LED 18 emits light that interacts with the indicator molecules in the matrix layer 14 (col. 6, lines 26-35). Alternatively, the fluorescent indicator molecules 16 can be coated directly on the surface of the sensor body (col. 6 lines 45-46). In contrast, sensors according to embodiments of the instant invention detect externally administered fluor-analytes, *e.g.*, analytes delivered systemically or locally, such as via injection, IV, catheter, and the like. That is, the fluorescence is from an exogenous source or source other than the sensor, *e.g.*, and the administered fluor-analyte(s) generates the detected fluorescence in response to the emitted excitation light, rather than a coating or matrix on the sensor body. *See, e.g.*, pp. 35-39 and particularly, p. 39, lines 1-5 of the pending application.

Claim 43 has been amended to clarify that the fluorescent analyte is administered from a source other than the at least one sensor. Claim 105 recites

that the sensor is configured to detect fluorescence that is administered remote from the sensor itself or from a source that is independent of the sensor.

Applicant respectfully submits that Claims 43 and 105 claim a sensor that is very different from that of Colvin and that Colvin fails to teach or suggest at least the emphasized features and requests that the anticipation rejection in view of Colvin be withdrawn.

IV. U.S. Patent Application Publication 2004/0054385 to Lesho et al ("Lesho")

The Action also rejects Claims 43-45, 54-56, 59-61 and 105 as being anticipated by Lesho. However, Lesho, while implantable, is deficient in that, like Colvin, it proposes indicator molecules on the surface of the sensor body or in the matrix layer (para. 6, 42, 52). Accordingly, per the discussion above with respect to Colvin, Applicant respectfully requests that this rejection also be withdrawn.

V. Shults in view of Stavridi

The Action rejects Claims 43, 44, 46, 47 51, 52-55, 60, 61, 69-71, 73, 75-77, 85, 88, 105 and 106 as being obvious over Shults in view of Stavridi. The Action concedes that Shults fails to teach that the excitation light is generated by a laser diode of a specific intensity and includes a detector with a filter, but alleges that the probe of Stavridi teaches these features.

As noted above, Shults and Stavridi are directed to detecting glucose. Shults notes the deficiencies of Stavridi as it is not configured as an implantable device. Shults states that to implement a fluorescence sensor such as Stavridi as an implantable device by using a biological filtrate or membrane (para. 56, 57) in a manner that allows a "continuous supply of biological glucose" to provide a stabilized sample volume for detection. Shults also states that the fluorescence sensor would include a source of radiation and fluorescent sensing molecules in the device to detect the presence of the analyte (para. 58) (apparently per the teachings of Colvin).

Notably, however, as also noted above, Stavridi proposes fluorescence in a lower and narrow band range to cause the glucose to fluoresce (Abstract and col. 2, col. 3, col. 5). Even

combined, Shults and Stavridi fail to teach or suggest the claimed operational features of detecting an administered fluor-analyte using a **fluorescence** excitation wavelength for the flour-analyte of about 400 nm or greater, as these excitation wavelengths are outside the characteristic spectral peak of glucose (Stavridi, col. 2, lines 5-6). Further, as each of the Shults and Stavridi references are directed to measuring glucose which is naturally in the body, they also teach away from detecting an administered fluor-analyte, which is time sensitive and the intensity of which varies greatly (to zero) relative to the time of administration of the analyte rather than a continuous supply per glucose in the body.

Also, Applicant respectfully submits that Shults (modified with the fluorescence sensor configuration of Stavridi) is configured to monitor glucose in a blood, plasma or interstitial fluid that is in the filtrate or membrane on the sensor. This is in further contrast to embodiments of the invention (as recited in Claims 44, 51 and 105), as the sensor(s) can project light that is able to penetrate tissue at distances of at least several millimeters away from the sensor typically several millimeters to about 20 mm, as discussed at page 38 of the application.

The Action alleges that the penetration depth is interpreted "in the absence of evidence to the contrary" that the laser diode of Stavridi would inherently have this range. Applicant respectfully disagrees. Rather, as Shults modified Stravridi, there is no need to penetrate tissue as the filter/filtrate is where the sensing is carried out, and it is not at all clear that the light source and energy level of the implantable sensor proposed by Shults would be able to do so.

Applicant respectfully submits that Shults and Stavridi combined, teach away from projecting the excitation light into local tissue at least 2 mm, much less at about 20 mm as recited in some claims, as the implantable sensor of Shults and Stavridi require a filtrate or membrane on the sensor body to detect glucose filtered out in the filter, no detection in subsurface or depths of local tissue is needed. Rather, Shults/Stavridi detect the sample in the filtrate on the sensor body whereby the glucose body fluid is filtered to remove interfering molecules.

In addition, Shults is directed at measuring glucose in a continuous supply, while embodiments of the invention are dormant between active monitoring periods proximate in time with a respective therapeutic treatment (*see, e.g.*, new Claim 117 and Figure 13E, pp. 28-29).

In view of the foregoing, Applicant respectfully submits that the claims are patentable over Shults and Stavridi and requests that these rejections be withdrawn.

VI. Colvin in view of Shults, Stavridi and Lesho

The Action rejects Claims 43-47, 51-88, 105 and 106 as being obvious based on the combination of these four references. However, as discussed above, Colvin and Lesho propose indicator molecules on the surface of the sensor body or in the matrix layer. Each of these references teach away from a system where the sensor does not provide a coating or matrix providing the fluorescence.

Applicant respectfully submits that properly combined, the sensor of Shults would be modified to include the coating or matrix of fluorescent indicator molecules 16 of Colvin or Colvin would include a filtrate layer over the matrix and detect glucose using the excitation wavelengths of Stavridi. Applicant respectfully submit that even combined, the references fail to teach or suggest at least the detection of fluorescence generated by externally administered fluor-analytes in the claimed excitation range.

Further, as noted by the Action, Lesho proposes a duty cycle of 50%. The Action alleges that it would have been obvious to vary this duty cycle because it is known to vary the duty cycle to determine analyte concentration (citing para. 74). However, Lesho merely describes a square wave operation whereby the capacitor charge times can vary, affecting the duty cycle, rather than an affirmative operational feature as claimed. The low duty cycle 1-10% helps with inhibiting quenching of the response in local tissue (p. 39, 40). Further, as Lesho employs an integrated matrix for the fluorescence, there appears to be less downside to quenching in subsurface tissue. Applicant respectfully submits that even combined, the references fail to teach or suggest the claimed low duty cycle (*see, e.g.*, Claim 80).

VII. Shults in view of Stavridi in view of Mayinger (Am. J. Gastroent., 2001, 9, p. 2116-2621) ("Mayinger")

Claims 43, 44, 46-55, 60, 61, 69-71, 73, 75-77, 85, 88, 105 and 106 stand rejected as being obvious over the three noted references. However, as noted above, both Shults and Stavridi are directed to detecting glucose. Mayinger is directed to *in vivo* differentiation of normal and neoplastic human tissue. The Action concedes that Mayinger fails to disclose an implantable fluorescence detection device (Action, p. 15), but alleges that it would have been obvious to incorporate the [glucose] sensor taught by Stavridi in the telemetrically operated device of Shults and to use the implantable [glucose] sensors of Shults and Stavridi to detect cancer because Mayinger states that *in vivo* fluorescence measurements have been used for such purposes.

However, the instant application does not claim detecting cancer. Rather, according to some embodiments, the sensors are used after diagnosis to monitor known cancer treatment sites (tumor sites) in the body to assess therapeutic reactions, delivery and/or uptake and retention of an analyte, receptiveness to therapy, confirmation of delivery (and/or delivered dose) of a chemotherapeutic agent or pharmacokentics/dynamics other cellular/tissue response. Thus, even combined, these references fail to teach or suggest monitoring local tissue for fluor-analytes at a tumor treatment site.

Further, it would not appear to be desirable to place an implantable device into a subject to detect or diagnose cancer, as a temporary short time device would appear to be sufficient for this purpose. Further, Shults, Stavridi and Mayinger all fail to teach or suggest administering a fluorescent analyte to be used in the detecting at the local tissue.

Applicant respectfully submits that the claims are patentable over this combination of references.

VIII. Other

Claims 70, 84 and 106 have been amended to recite the sensor can also include an optical filter inside the body of the sensor (as shown, for example, in Figure 12).

IX. New Claims

Applicant has added new claims to more fully claim embodiments of the invention. Applicant respectfully submits that the claims are supported by the application and are patentable over the cited prior art. Examples of support include:

- Claim 107, *see* pp. 38 and 40,
- Claim 108, *see*, pp. 28, 30 and 31,
- Claims 109, *see* pp. 14 and 15,
- Claim 110, *see* pp.22, 26 and 39,
- Claim 111, *see* pp. 23-25,
- Claim 112, *see*, p. 28,
- Claim 113, *see*, pp. 28, 30 and 31,
- Claim 114, *see* p. 40,
- Claim 115, *see* Figure 1A and pp. 9-11,
- Independent Claim 116, *see*, p. 28,
- Independent Claim 117, *see*, pp. 23-25, 29, 38 and 40,
- Claim 118, *see*, pp. 21, 22 and 27,
- Claim 119, *see*, p. 22,
- Claim 120, *see* pp. 15, 21, 23 and 31,
- Claim 121, *see* p. 15,
- Claim 122, *see* p. 39, and
- Claim 123, *see* p. 15.

The new independent claims are restated below with novel features emphasized for ease of discussion.

117. A detection system for detecting fluorescence in a patient's body associated with an administered fluorescently labeled chemotherapeutic agent, the detection system comprising:

at least one implantable fluorescence sensor configured for *in vivo* operation, the at least one sensor being configured to emit a fluorescence excitation light signal between about 400 nm to about 900 nm and to

detect fluorescence from a fluorescently labeled chemotherapeutic agent in localized tissue in the body in response to the emitted excitation light signal, at least intermittently, over an active monitoring period of time extending for at least about 24 hours after administration of the fluorescently labeled chemotherapeutic agent, wherein the at least one sensor is dormant between successive active monitoring periods; and

a processor operably associated with the at least one implantable sensor configured to direct output of the excitation signal to local tissue and to receive fluorescence intensity signal data associated with the locally detected fluorescence of the chemotherapeutic agent from the at least one sensor, wherein said processor includes computer program code for monitoring fluorescence intensity over time associated with one or more of the uptake and retention of the fluorescently labeled agent in target localized tissue at a plurality of points in time over at least one monitoring period to generate a time response profile.

119. A detection system for monitoring pharmacokinetics and/or pharmacodynamics in a subject associated with an administered fluorescently labeled analyte, the detection system comprising:

at least one fluorescence sensor configured for *in vivo* operation, the at least one sensor being configured to emit a fluorescence excitation light signal at a wavelength of at least about 400 nm and to detect fluorescence from the fluorescently labeled analyte in localized tissue at a target site in the body in response to the emitted excitation light signal; and

a processor operably associated with the at least one sensor configured to direct output of the excitation signal to the target site and to receive the detected fluorescence intensity signal data, wherein said processor is configured to monitor fluorescence intensity of the fluorescently labeled analyte in the localized tissue at a plurality of points in time over at least one monitoring period to determine the pharmacokinetics and/or pharmacodynamics at the target site.

123. A system for determining a phenotypic response of a patient to a selected drug therapy, comprising:

at least one fluorescence sensor configured for *in vivo* operation, the at least one sensor being configured to emit a fluorescence excitation light signal at a wavelength of at least about 400 nm and to detect fluorescence from an administered fluorescently labeled therapeutic agent in localized tissue at a target site in the body in response to the emitted excitation light signal; and

a processor operably associated with the at least one sensor configured to direct output of the excitation signal to the target site and to

receive the detected fluorescence intensity signal data, wherein said processor is configured to monitor fluorescence intensity of the fluorescently labeled therapeutic agent in the localized tissue at a plurality of points in time over at least one monitoring period and predict a phenotypic response of the patient to the therapeutic agent at the target site.

Applicant respectfully requests entry and consideration of the new detection system claims.

CONCLUSION

Applicant respectfully submits that this application is now in condition for allowance, which action is requested. If any extension of time for the accompanying response or submission is required, Applicant requests that this be considered a petition therefor. The Commissioner is hereby authorized to charge any additional fee, which may be required, or credit any refund, to our Deposit Account No. 50-0220.

Respectfully submitted,

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